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Review

The role of lamina cribrosa cells in optic nerve head fibrosis in glaucoma

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ABSTRACT

Glaucoma is a chronic progressive optic neuropathy. There are extracellular matrix (ECM) changes associated with optic disc cupping in the optic nerve head (ONH) and subsequent visual field defects. The primary risk factor for onset and progression of glaucoma is raised intraocular pressure (IOP). Elevated IOP causes deformation at the ONH specifically at the lamina cribrosa (LC) region where there is also deposition of ECM causing the LC to initially undergo thickening and posterior migration with eventual shearing and collapse of the LC plates leading to a thin fibrotic connective tissue structure/scar. Cells that populate the LC region of the ONH are those cells that are positive for GFAP (the astrocytes) and those negative for GFAP (the LC cells). The LC cell plays an integral role in ECM remodelling producing ECM when exposed to high level mechanical stretch, TGF- β1 and a hypoxic environment.

1. Introduction

Glaucoma, a chronic optic neuropathy, is the second leading cause of irreversible blindness worldwide, thought to affect 60 million people (Kelliher et al., 2006; Quigley and Broman, 2006). In the western world, glaucoma affects 1–2% of the population over the age of 40 and the prevalence rises to 5% of those aged 70 years and over. There are characteristic extracellular matrix (ECM) changes associated with optic disc cupping in the optic nerve head (ONH) and subsequent visual field defects. The primary risk factor for onset and progression of glaucoma is raised intraocular pressure (IOP) (Author anonymous 1998a, 1998b; Gordon et al., 2002; Leske et al., 2004; Spry et al., 2005). IOP is defined as the rate of aqueous humour production by the ciliary body, and the aqueous humour resistance via the iridocorneal tissues, trabecular meshwork and Schlemms canal (SC) and to a lesser extent the uveoscleral pathway. IOP is generated in the anterior eye via the aqueous humour circulation system. The aqueous humour is secreted by the cilary epithelium and flows to the anterior chamber to leave through the trabecular meshwork (TM) outflow pathways (Tamm, 2009). In primary open angle glaucoma (POAG) the resistance to outflow increases (Johnson et al., 2002) in the TM, particularly in the juxtacanalicular connective tissue (JCT) region culminating in elevated IOP (Johnson, 2006). The TM and SC provide the major route for outflow of the aqueous humour from the eye and it is here responsible for the increased IOP associated with POAG due to increased outflow resistance (Maepea and Bill, 1992; Moses, 1977). Cellular contraction and relaxation of TM and SC cells are important factors in the maintenance of normal aqueous humour outflow facility and agents that can alter contraction can change outflow rates (Epstein et al., 1987, 1999; Rao et al., 2005; Tian et al., 2000; Tian and Kaufman, 2005; Wiederholt et al., 2000; Yu et al., 2008b). Various studies have also established the endothelial cell of the SC as a reactive but variable mechanical component of the aqueous humour outflow pathway (Johnson, 2006; Overby et al., 2014; Zhou et al., 2011). In POAG, elevation of IOP in turn leads to deformation at the optic nerve head (ONH) specifically at the lamina cribrosa (LC) region where there is also deposition of extracellular matrix (ECM) molecules such as collagen and fibronectin. The connective tissue changes in POAG affects the TM and LC and it has been hypothesized that the TM and LC are biochemically similar tissues and that the cells cultured from the two are very similar (Clark et al., 1994; Hernandez et al., 1987; Kirwan et al., 2009; Morrison et al., 1989; Rehnberg et al., 1987; Steely et al., 2000; Wilson et al., 1993; Yun et al., 1989). The LC ECM is markedly disturbed in POAG leading to a remodelled and fibrotic tissue that is morphologically and quantitatively different from the

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Abbreviations

AKR1C1	aldo-keto reductase family 1 member C1
α-SMA	alpha-smooth muscle actin
BMP7	bone morphogenetic protein
BNIP3	BCL2/adenovirus EIB 19 kDa protein intertacing protein 3
$[Ca^{2+}]_I$	intracellular calcium
Col	Collagen
CTGF	connective tissue growth factor
DDRI/TrkE	discoidin domain receptor family member 1
ECM	extracellular matrix
ESM-1	endothelial specific molecule 1
FB-1	fibrillin
FN	fibronectin
GCLC	Glutamate cysteine ligase catalytic subunit
IOP	intraocular pressure
IL-11	interleukin 11
JCT	juxtacanalicular connective tissue
LC	lamina cribrosa
MDA	malondialdehyde
MIF	macrophage migration inhibitory factor
MMP	matrix metalloproteinase
NCX	sodium/calcium exchanger
ONH	optic nerve head
PAI-1	plasminogen activator inhibitor 1
PDGF-alpha	platelet derived growth factor
PMCA	plasma membrane Ca^{2+}/ATPase
POAG	primary open angle glaucoma
PXF	pseudoexfoliation
PXFG	pseudoexfoliation glaucoma
SERCA	sarco-endoplasmic reticulum Ca^{2+}/ATPase 3
TGF-β	transforming growth factor beta
TIMP1	tissue inhibitor of matrix metalloproteinase
TM	trabecular meshwork
TSP2	thrombospondin 2
VEGF	vascular endothelial growth factor

normal ONH (Burgoyne et al., 2005; Hernandez et al., 1990; Hernandez and Pena, 1997; Jonas et al., 2003; Quigley, 2011; Yang et al., 2011a, 2011b).

The LC region of the ONH consists of perforated fibroelastic plates through which the unmyelinated retinal ganglion cell axons pass through before they converge as the optic nerve (Anderson, 1969). A major area of interest centres on identifying the cell (or cells) responsible for producing this aberrant lamina cribrosa ECM (Hernandez, 2000). Cells that populate the LC are those cells that are positive for GFAP (the astrocytes) and those negative for GFAP (the LC cells) (Hernandez et al., 1988). A third type of cell, microglia have also been located in the LC region of the ONH and have been shown to be activated in the human glaucomatous ONH where it is proposed that they may have detrimental consequences (Yuan and Neufeld, 2001). Morphologically, the LC cells are broad, flat and polygonal as opposed to the star-shaped astrocytes (Hernandez et al., 1988). The LC cells are localised to the lamina cribrosa region and are situated within or between the cribriform plates, whereas the astrocytes are located throughout the ONH and separate the retinal ganglion cells axons from the aforementioned cribriform plates (Hernandez, 2000). The LC cell is of relevance as it bears similarities to myofibroblastic cells known to be responsible for fibrotic disease development elsewhere in the human body (Naugle et al., 2006). These similarities include constitutive expression of alpha-smooth muscle actin (α-SMA), elastin, collagen 1 and fibronectin (Lambert et al., 2001). Results from our laboratory have shown that the LC cell plays an integral role in ECM remodelling producing ECM when exposed to high level mechanical stretch (Kirwan et al., 2005a) and treatment with TGF- β1 (Kirwan et al., 2005b). TGF- β1 is a well known mediator of ocular wound healing (Cordeiro et al., 2000; Picht et al., 2001) and its role in the pathogenesis of glaucoma has been extensively investigated (Fuchshofer, 2010; Fuchshofer et al., 2005; Fuchshofer and Tamm, 2011; Kottler et al., 2005). Furthermore, many dysfunctional cellular processes are associated with LC cells from glaucoma donors as outlined in Table 1. We have previously reported the differential expression of fibrotic genes in LC cells obtained from donors with and without POAG (Kirwan et al., 2009) (Table 2) and Hernandez et al. showed that it is the LC which undergoes fibrosis and mechanical failure in POAG (Hernandez et al., 1990). These laminar plates contain ECM such as elastin and collagen I, III, V and VI and it is here the nerve axons degenerate in parallel with the apoptotic cell death of retinal ganglion cells and results in progressive visual field loss. Axonal degeneration may be caused by blockade of the anterograde and retrograde axonal transport systems at the level of the LC leading to deprivation of neurotrophic signals (Quigley, 2011) and is accompanied by local remodelling of the ECM in the ONH particularly evident in the LC region (Burgoyne et al., 2005). In experimental monkey glaucoma, the LC undergoes thickening and posterior migration (Yang et al., 2011a, 2011b) in the

Table 1
Dysfunctional Cellular processes associated with LC cells from glaucoma donors.

Cellular process	Glaucoma *v* normal LC cells	
Antioxidant capacity	MDA↑	
	AKR1C1↓/GCLC↓	McElnea et al. (2011)
Calcium homeostasis	Maxi K^+↑	Irnaten et al. (2013)
	$[Ca^{2+}]_I$ levels↑	McElnea et al. (2011)
	PMCA↓/NCX↑	
	SERCA↑	
Mitochondrial function	Mitochondrial membrane potential↓	McElnea et al. (2011)

MDA = malondialdehyde, AKR1C1 = Aldo-keto reductase family 1 member C1/GCLC = Glutamate cysteine ligase catalytic subunit, $[Ca^{2+}]_I$ = intracellular calcium, PMCA = plasma membrane Ca^{2+}/ATPase, NCX = sodium/calcium exchanger, SERCA = sarco-endoplasmic reticulum Ca^{2+}/ATPase 3.

Table 2
Differentially expressed extracellular matrix genes in POAG LC cells compared to normal LC cells.

Gene	Signal log ratio
Osteoblast specific factor 2 (periostin)	3.0
Tissue inhibitor of metalloproteinase 3 (TIMP-3)	1.3
Chondroitin sulfate proteoglycan 3 (versican)	1.2
Sparc/osteonectin	1.1
Thrombospondin 1	0.8
Lysyl oxidase	0.7
Transforming growth factor beta-induced, 68 kDa	0.6
Collagen Iα1	0.6
Collagen Vα1	0.5